

MODES OF INHERITANCE IN MAN

Prof. Arjumand S. Warsy
Department of Biochemistry, College of Science
King Saud University, Riyadh

Introduction

- The pattern in which a disorder is transmitted from one generation to another must be determined in order to investigate the genetics of the disorder. This also enables giving proper advice to the members of the family about transmission of the disorder (i.e. genetic counselling).
- This involves taking "family history".
- The symbols used when constructing a family tree are given in Figure I.

I. Mendelian Inheritance:

- Single gene traits exhibit 'unifactorial' or Mendelian inheritance. To date, over 6000 such traits or disorders have been identified.
- The pattern of inheritance depends on whether the trait or disorder is located on the autosomes or the sex chromosomes, and whether the phenotype is dominant or recessive (Note: Genes are classified as recessive or dominant on the basis of their phenotype expression)
- The modes (patterns) of inheritance are:
 - Autosomal:
 - Autosomal dominant
 - Autosomal recessive
 - Sex linked:

- X linked:
 - X linked dominant
 - X linked recessive
- Y linked

Autosomal Inheritance:

- The gene is present on the 44 autosomes which comprise of 22 homologous pairs of chromosomes.
- Inheritance is the same in males and females.
- If the trait is expressed in heterozygotes, it is dominant, while if it is expressed in only the homozygous state, it is recessive. In some cases both alleles may be seen in heterozygotes and in these cases the trait is codominant.

(i) Autosomal dominant (AD) inheritance:

- The trait is expressed in heterozygotes.
- The trait never skips a generation.
- Affected parent transmits the condition equally to both male and female progeny.
- Unaffected persons do not transmit the condition.
- If one parent is heterozygote for the AD trait the chance that a child will have the disease is 1 in 2: i.e. 50%.
- If one parent is homozygous for the AD trait, then 100% of the children will have the disease.
- Family tree of AD disorder is shown in Figure I.

Examples of AD disease:

Over 3700 AD traits are shown e.g.:

- Familial hypercholesterolaemia
- Huntington disease
- Myotonic dystrophy
- Adult polycystic kidney disease
- Neurofibromatosis
- Polydactyly
- Dominant congenital deafness
- Others.

○ Special features of AD disorders:

- Vertical pedigree pattern
- Pleiotropy. AD disorders may affect only one organ or part of the body. Some manifest in different systems of the body in a variety of way i.e. pleiotropy e.g. patients with tuberous sclerosis may have hearing difficulty, epilepsy and a facial rash.
- Variable expressivity. AD disorder may show individual variation in clinical expression.
- Reduced penetrance. Individuals within the family with the same mutation have different clinical expression. In some the mutation may go undetected (non-penetrance). The difference in penetrance results from modifying effect of other genes and environmental factors. In some cases the onset is age-dependent.
- New mutations. A sudden unexpected appearance of a condition in an offspring without its presence in the parents, is often due to new dominant mutations. This may be due to increased age of the father.
- Codominance. Some AD traits are codominant and are expressed in heterozygote state e.g. AB blood groups.

(ii) Autosomal Recessive Inheritance:

- The trait is expressed only in homozygotes.
- Parents of the affected individual are carriers (heterozygous) of the trait, and are perfectly healthy and normal.
- If both parents are carriers, the chance of having an affected child is 1 in 4 i.e. 25%.
- All children of an affected person are carriers.
- The affected individuals in a family are usually in a single siblings i.e. brothers and sisters - Horizontal inheritance.
- Often parents of an affected individual are consanguineous.
- Family tree of an AR disorder is shown in Figure 2.

Examples of AR Diseases:

Over 1600 AR traits are known e.g.

- Sickle cell anaemia
- Thalassaemia
- Tay Sachs disease
- Albinism
- Cystic fibrosis
- Severe combine immunodeficiency

- Gauchers disease
- Phenylketonuria
- Recessive blindness
- Others.

○ Special features of AR disorders:

- Horizontal pedigree pattern
- Consanguinity
- Pseudodominance: If a homozygous for an AR marries a carrier of the same disorder, the offsprings have 1 in 2 (50%) chance of being affected i.e. pseudodominance.
- Genetic heterogeneity: A number of disorders may be inherited in an AR, AD and X linked manner. This is "genetic heterogeneity". In addition, a disorder inherited in the same manner can be due to mutations in more than one genes. 'Locus heterogeneity' if two or more genes can show the same phenotype but are in fact genetically distinct. Offspring of parents homozygous at different loci are 'double heterozygotes'.
- Compound heterozygotes: If two different allelic mutations occur at the same locus. More individuals affected by AR disorders may be compound heterozygotes.

(iii) Autosomal Codominant Inheritance:

Some alleles are codominant and both alleles are expressed in heterozygotes e.g.

- Blood groups: ABO, Buffy, Kel etc.
- Acid phosphatase, adenylate kinase
- Haptoglobin
- HLA

Sex Linked Inheritance

Genes are located on the sex chromosomes and the pattern of inheritance differs in the males and females. This type of disorders are either X or Y linked:

(a) Y-linked or holandric inheritance:

The trait is located on the Y-chromosome and is inherited from the fathers to their sons only. Affected fathers always have affected sons but no affected daughters.

- e.g.
- Hairy ears
 - Webbed toes
 - H-Y histocompatibility antigen.
 - Gene involved in spermatogenesis

(b) X-Linked Inheritance:

The trait is present on the X chromosome. Since male have only one X chromosome and female have two, the pattern of inheritance differs in the males and the females and depends on whether the trait is recessive or dominant:

(i) X-Linked Recessive (XR)

- The trait on the X chromosome is recessive
- Always manifests in male (hemizygotes)
- Manifests only in homozygous females while a heterozygous female is a carrier (healthy)
- A healthy heterozygous female has 50% affected sons and 50% carrier daughters.
- An affected male has no affected sons but all daughters are carriers.
- An affected male transmits the traits through his daughters (carriers) to his grandsons. This is referred to as "Knight's Move" pedigree pattern of affected males.
- If the male is affected and female is carrier then 50% of daughters and 50% sons are affected. 50% daughters are carriers and 50% sons are normal.
- An unaffected male never transmits the condition.
- Family tree of an XR disorder is shown in Figure 3.

Examples of X-Linked Recessive Disorders:

Over 370 XR traits are known. They differ in their frequency in different populations:

- Becker Muscular Dystrophy
- Haemophilia A & B
- Fragile X-syndrome
- Colour blindness
- Duchenne Muscular Dystrophy
- Glucose-6-phosphate dehydrogenase deficiency
- Lesch Nyhan syndrome

Special Features of XR Disorders:

- Lyon Hypothesis: Often carrier females have a mosaic phenotype, with a mixture of mutant and normal alleles. This is explained on the basis of Lyons hypothesis (Mary Lyon 1961, 1962). According to this:
 - (a) Only one X chromosome is active in somatic cells, the second is condensed and inactive and appears as Barr body in inter phase cells.
 - (b) Inactivation of one X chromosome occurs in early embryonic-life.

- (c) In any one female somatic cell, inactive X may be maternal or paternal (entirely a matter of chance).

This leads to:

- Dosage compensation
 - Variability of expression in heterozygotes
 - Mosaicism
- Dosage compensation: Although much of an X is inactivated some segments at the distal region of the short arm remain active. These regions are known as 'pseudoautosomal regions' as they have matching sequences on Y chromosomes by means of which the X and Y pair in meiosis. These gene escape dosage compensation.
- Variable expression in heterozygous females: Heterozygous females may have clinical expression ranging from entirely normal to full manifestation of the defect. This results from the inactivation of the X which has the normal allele. This gives variability of expression.
- X-Linked Dominant (XD)
- The X-linked phenotype is expressed in heterozygotes:
- All the daughters and none of the sons of an affected male are affected.
 - Each child of an affected female has a 50% chance of inheriting the phenotype.
 - The disorders are more frequent in females than males.
 - The expression of the disorder is generally milder in females as they are usually heterozygotes.
 - Direct male to male transmission cannot occur.
- A family pedigree of XD inheritance is shown in Figure 4.

Examples of XD Disorders:

- These disorders are not common:
- X-linked hyperphosphatemic rickets (Vit. D resistant rickets)

- Ornithine transcarbamylase deficiency
- Rett Syndrome
- Xg blood group

Non Mendelian Inheritance

Some disorders do not follow Mendelian inheritance. The following mechanisms are used to explain this phenomenon.

- Anticipation: Some AD trait presentation in children is at an earlier age than the parents or the disease occurs with increasing severity in subsequent generations. This phenomenon is known as "Anticipation".
- This is observed in Huntington's disease and in myotonic dystrophy. In the former there is an expansion of a CAG triplet repeat at 5' untranslated end of the Huntington's disease gene, while a GTG triplet is increased at the 3' untranslated end of myotonic dystrophy. The higher the expansion the more severe the disease.
- Mosaicism: Due to some error during mitosis an individual or a particular tissue of the body, may have more than one cell line or type. Mosaics of somatic and germ cells can account for unusual patterns of inheritance:
 - Somatic mosaics - proportion of somatic cells are mutated.
 - Gonadal Mosaics - proportion of germ cells are mutated. Thus parents may be entirely normal to a disorder (AD or XR) yet more than one of their children are affected. This can be explained by Gonadal Mosaicism i.e. a proportion of the gonadal cells are affected.
 - Uniparental Disomy:
 - If both chromosomes are inherited from the parent, due to error during meiosis I or II (originally trisomy, later due to loss of one chromosome a disomic state appears) e.g.
 - Cases of CF in which only mother was a carrier.
 - Another with haemophilia had affected son.
 - Genomic imprinting: A gene whether inherited from the mother or father, may show differences in expression. This "parent of origin" effect is known as genomic imprinting. This is observed in mental handicap with Prader-Willi and Angelman syndrome.

III. Mitochondrial Inheritance:

- Disorders which occur in both males and females, but are transmitted only through females, as shown in the family pedigree (Figure 5).

- There is an exclusive maternal contribution of mitochondrial DNA to offsprings e.g.
 - A hereditary blindness
 - Leber's optic atrophy
 - Kearus-Sayre syndrome
 - Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.

